

Human and Murine Tissue-Engineered Colon Exhibit Diverse Neuronal Subtypes and Can Be Populated by Enteric Nervous System Progenitor Cells When Donor Colon Is Aganglionic.

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Public Summary:

Tissue-engineered colon (TEC) might potentially replace absent or injured large intestine, but the enteric nervous system (ENS), a key component, has not been investigated. In various enteric neuropathic diseases in which the TEC is derived from aganglionic donor colon, the resulting construct might also be aganglionic, limiting tissue engineering applications in conditions such as Hirschsprung disease (HD). We hypothesized that TEC might contain a diverse population of enteric neuronal subtypes, and that aganglionic TEC can be populated by neurons and glia when supplemented with ENS progenitor cells in the form of neurospheres. **MATERIALS AND METHODS:** Human and murine organoid units (OU) and multicellular clusters containing epithelium and mesenchyme were isolated from both mouse and human donor tissues, including from normally innervated and aganglionic colon. The OU were seeded onto a biodegradable scaffold and implanted within a host mouse, resulting in the growth of TEC. Aganglionic murine and human OU were supplemented with cultured neurospheres to populate the absent ENS not provided by the OU to rescue the HD phenotype. **RESULTS:** TEC demonstrated abundant smooth muscle and clusters of neurons and glia beneath the epithelium and deeper within the mesenchyme. Motor and afferent neuronal subtypes were identified in TEC. Aganglionic OU formed TEC with absent neural elements, but neurons and glia were abundant when aganglionic OU were supplemented with ENS progenitor cells. **CONCLUSION:** Murine and human TEC contain key components of the ENS that were not previously identified, including glia, neurons, and fundamental neuronal subtypes. TEC derived from aganglionic colon can be populated with neurons and glia when supplemented with neurospheres. Combining tissue engineering and cellular replacement therapies represents a new strategy for treating enteric neuropathies, particularly HD.

Scientific Abstract:

PURPOSE: Tissue-engineered colon (TEC) might potentially replace absent or injured large intestine, but the enteric nervous system (ENS), a key component, has not been investigated. In various enteric neuropathic diseases in which the TEC is derived from aganglionic donor colon, the resulting construct might also be aganglionic, limiting tissue engineering applications in conditions such as Hirschsprung disease (HD). We hypothesized that TEC might contain a diverse population of enteric neuronal subtypes, and that aganglionic TEC can be populated by neurons and glia when supplemented with ENS progenitor cells in the form of neurospheres. **MATERIALS AND METHODS:** Human and murine organoid units (OU) and multicellular clusters containing epithelium and mesenchyme were isolated from both mouse and human donor tissues, including from normally innervated and aganglionic colon. The OU were seeded onto a biodegradable scaffold and implanted within a host mouse, resulting in the growth of TEC. Aganglionic murine and human OU were supplemented with cultured neurospheres to populate the absent ENS not provided by the OU to rescue the HD phenotype. **RESULTS:** TEC demonstrated abundant smooth muscle and clusters of neurons and glia beneath the epithelium and deeper within the mesenchyme. Motor and afferent neuronal subtypes were identified in TEC. Aganglionic OU formed TEC with absent neural elements, but neurons and glia were abundant when aganglionic OU were supplemented with ENS progenitor cells. **CONCLUSION:** Murine and human TEC contain key components of the ENS that were not previously identified, including glia, neurons, and fundamental neuronal subtypes. TEC derived from aganglionic colon can be populated with neurons and glia when supplemented with neurospheres. Combining tissue engineering and cellular replacement therapies represents a new strategy for treating enteric neuropathies, particularly HD.

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